1: Cancer Immunol Immunother. 1990;32(3):185-90. Related Articles, Links

A phase II trial of murine monoclonal antibody 17-1A and interferon-gamma: clinical and immunological data.

Saleh MN, LoBuglio AF, Wheeler RH, Rogers KJ, Haynes A, Lee JY, Khazaeli MB.

Comprehensive Cancer Center, University of Alabama, Birmingham 35294.

A group of 15 patients with metastatic colorectal adenocarcinoma received a combination of interferon gamma (0.1 mg/m2, days 1-15) and the murine monoclonal antibody 17-1A (400 mg, days 5, 7, 9 and 12). The treatment was tolerated with minimal toxicity. Of the 14 evaluable patients, 13 developed human antibody to murine 17-1A, with 11 patients demonstrating antibody to the variable region of 17-1A (anti-idiotype). Antibody to the variable region was inhibited by 17-1A but not by mouse immunoglobulin. Sera from patients with substantial anti-idiotype reactivity were capable of inhibiting the binding of murine 17-1A to antigen expressing LS174-T cells thus indicating the presence of antibody directed against the 17-1A combining site (mirror-image anti-idiotype). The median survival of the whole group was 56 weeks and there was no correlation between clinical response/survival and the development of anti-idiotype antibody.

Publication Types:
- Clinical Trial

PMID: 2126988 [PubMed - indexed for MEDLINE]

1: Cancer Immunol Immunother. 1990;31(4):231-5. Related Articles, Links

Granulocyte-monocyte colony-stimulating-factor augments the interleukin-2-induced cytotoxic activity of human lymphocytes in the absence and presence of mouse or chimeric monoclonal antibodies (mAb 17-1A).

Masucci G, Ragnhammar P, Wersall P, Mellstedt H.

Department of Oncology, Radiumhemmet, Immunologic Research Laboratory, Karolinska Hospital, Stockholm, Sweden.

Blood lymphocytes stimulated for 96 h with interleukin-2 (IL-2; 100 BRMP U/ml) (lymphokine-activated killer, LAK, cells) or granulocyte-monocyte colony-stimulating-factor (GM-CSF) (10 ng/ml) became cytotoxic for Daudi cells. IL-2 was significantly more effective than GM-CSF. Only IL-2-activated cells killed SW948 (a human colorectal carcinoma cell line) while GM-CSF-stimulated cell did not. GM-CSF and IL-2 acted synergistically in a dose-dependent fashion for induction of a highly effective cytotoxic cell population (IL-2/GM-CSF cells). Il-2/GM-CSF cells were statistically significantly more effective than LAK cells in lysing Daudi cells and SW948 (P less than 0.05). The enhancing effect was most pronounced during the first 48-96 h of activation. Incubation periods longer than 192 h did not contribute to augmented cytotoxicity. The combination of IL-2 and GM-CSF significantly increased the number of CD25+ cells compared to IL-2 and GM-CSF alone. Furthermore, IL-2/GM-CSF cells were significantly more effective in antibody-dependent cellular cytotoxicity assays (SW948 + mAb 17-1A) than LAK cells. The chimeric mAb 17-1A was significantly more effective in tumor cell lysis than the mouse mAb. Thus, combination of various biological therapeutics might be a way to enhance their antitumoral effects.

PMID: 2199042 [PubMed - indexed for MEDLINE]

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☐ 1: Cancer Immunol Immunother. 1992;35(3):158-64. Related Articles, Links

Cytotoxic functions of blood mononuclear cells in patients with colorectal carcinoma treated with mAb 17-1A and granulocyte/macrophage-colony-stimulating factor.

Ragnhammar P, Masucci G, Frodin JE, Hjelm AL, Mellstedt H.

Department of Oncology (Radiumhemmet), Karolinska Hospital, Stockholm, Sweden.

Unconjugated monoclonal antibodies (mAb) may induce tumour regression in patients. The mechanisms of action are complex. Antibody-dependent cellular cytotoxicity (ADCC) is considered one of the effector functions. Augmentation of the killing capacity of cytotoxic cells may thus be a way to increase the therapeutic potential of mAb. Granulocyte/macrophage-colony-stimulating factor (GM-CSF) has been shown to enhance this function in vitro. Eighteen patients with metastatic colorectal carcinoma received GM-CSF (250 micrograms m-2 day-1 s.c.) for 10 days and a single infusion of the anti-(colon carcinoma) mAb 17-1A (mouse IgG2A) (400 mg) on day 3 of the cycle. The cycles were repeated once a month four times. Neutrophils, eosinophils, monocytes and lymphocytes increased significantly in a biphasic way. However, at the fourth cycle the rise in white blood cells was significantly lower compared to the preceding courses. ADCC (SW948, a human CRC cell line,+mAb 17-1A) or peripheral blood mononuclear cells (PBMC) was significantly (P less than 0.05) augmented by day 6 of a cycle and then declined gradually and, at the end of a cycle, the ADCC activity had returned to the pretreatment level. The spontaneous cytotoxicity of PBMC against the natural-killer-resistant cell line, SW948, varied in a similar way. During GM-CSF treatment there was also a significant increase in FcRI+ (CD64), FcRII+ (CD32), FcRIII+ (CD16) and CD14+ cells but not of CD56+ cells.

PMID: 1638551 [PubMed - indexed for MEDLINE]

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☐ 1: Clin Cancer Res. 1998 Aug;4(8):1921-9. Related Articles, Links

Immunopathology of metastases in patients of colorectal carcinoma treated with monoclonal antibody 17-1A and granulocyte macrophage colony-stimulating factor.

Shetye J, Ragnhammar P, Liljefors M, Christensson B, Frodin JE, Biberfeld P, Mellstedt H.

Department of Oncology/Pathology, Karolinska Hospital, Stockholm, Sweden.

Twenty patients with metastatic colorectal carcinoma were treated with a single infusion (400 mg) of a mouse monoclonal antibody (IgG2a) against the tumor-associated antigen CO 17-1A and with a daily injection of granulocyte macrophage colony-stimulating factor (GM-CSF) for 10 days. The cycle was repeated every month. Metastases from 5 of the 20 patients biopsied on days 1 and 10 of the first two treatment cycles were studied by immunohistochemistry. During treatment, neutrophils, monocytes, and T lymphocytes increased concordantly in the tumor as in the blood of the individual patient. Macrophages (CD68) and CD8+ T cells infiltrated the tumor glands and displayed TIA-1-reactive cytotoxic granules. Neutrophils were seen mainly in areas of necrosis. Activated (HLA-DR+) CD4+ T cells were usually abundant in the stroma. During treatment, few natural killer cells were found in the tumor, contrary to the marked increase seen in blood. Our observations indicate that GM-CSF markedly recruited activated, tumor-infiltrating leukocytes, possibly representing antibody-dependent cellular cytotoxicity and cytotoxic T effector cells. The notion that combined antibody and GM-CSF therapy may also promote a T-cell antitumor response is further supported and advocated by our findings. The study lends further support to combining GM-CSF with monoclonal antibody-based therapy.

Publication Types:
- Clinical Trial
- Clinical Trial, Phase II

PMID: 9717820 [PubMed - indexed for MEDLINE]

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1: Jpn J Cancer Res. 1990 Mar;81(3):266-71. Related Articles, Links

Influence of cocktails of labeled monoclonal antibodies on the localization of antibodies in human tumor xenografts.

Watanabe Y, Endo K, Saga T, Koizumi M, Sakahara H, Nakai T, Hosono M, Yao ZS, Kuroki M, Matsuoka Y, et al.

Department of Nuclear Medicine, Kyoto University Hospital.

In order to evaluate the usefulness of cocktails of labeled monoclonal antibodies (MoAbs) recognizing different antigen molecules to localize human cancer xenografts, we have compared the potential of three MoAbs recognizing representative cancer-associated CA 19-9, 17-1A and CEA antigens when administered alone or in combination. Specific binding of radioiodinated F(ab')2 fragments of these three MoAbs was observed to human colorectal cancer cell lines SW1116, LS180 and Co-3. The percentage of in vitro cell binding of a cocktail of any two MoAbs to cancer cells was equal to the average of those obtained with the two MoAbs alone. The three MoAbs were preferentially localized in tumor tissues xenografted in nude mice. When cocktails of any two MoAbs were used, the obtained tumor-to-normal tissue ratios and percent of injected dose per gram of tumor were between the levels obtained for each MoAb when administered alone, in all three tumors transplanted in nude mice. These data suggest that, although cocktails of labeled MoAbs recognizing different antigens may extend the spectrum of tumor specificities, their use does not improve the tumor localization ability of MoAb-conjugates.

PMID: 2112530 [PubMed - indexed for MEDLINE]

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1: J Immunother Emphasis Tumor Immunol. 1996 Jul;19 (4):245-56.

The role of monoclonal antibody affinity in tumor immunotherapy evaluated in in vivo models for minimal residual disease.

Velders MP, van Rhijn CM, Cornelissen IM, van Muijen GN, Briaire IH, Dohlsten M, Fleuren GJ, Warnaar SO, Litvinov SV.

Department of Pathology, Leiden University Hospital, The Netherlands.

To evaluate the role of affinity in monoclonal antibody (mAb)-mediated treatment of carcinomas, we compared the antibodies 17-1A and 323/A3 that bind with different affinities overlapping epitopes on the epithelial adhesion molecule Ep-CAM. This comparison was performed in several models for minimal residual disease in mice grafted with Ep-CAM transfected B16 melanoma cells originating from C57BL/6 mice. These cells were either grafted subcutaneously or injected intravenously into nude BALB/c mice, or grafted subcutaneously in immunocompetent C57BL/6 mice. In the BALB/c subcutaneous model, significant therapeutic results ($p < 0.05$) compared with the control mAb were obtained with both mAbs 17-1A and 323/A3. However, when treating lung metastases in nude BALB/c mice that had developed after intravenous injection of the B16/Ep-CAM tumor cells, only the high-affinity 323/A3 mAb could significantly ($p < 0.05$) reduce the number of metastases that appeared. In syngeneic C57BL/6 mice grafted subcutaneously with B16/ Ep-CAM cells, a single 323/A3 or 17-1A mAb injection had no effect, in contrast to that observed for the nude BALB/c mouse model. However, multiple injections of the 323/A3 mAb significantly ($p < 0.005$) reduced the mean tumor volume, although they did not prevent tumor development. The results show that in vivo antibody-mediated effector cell activation and subsequent tumor cell elimination is determined by mAb affinity and target antigen density. Therefore, treatment of minimal residual disease with high-affinity mAb 323/ A3 is expected to improve the clinical results obtained with mAb 17-1A.

PMID: 8877719 [PubMed - indexed for MEDLINE]